IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

VAN NEST et al.

Serial No.: 08/418,870 Group Art Unit: 1643

Filing Date: April 7, 1995 Examiner: D. Wortman

Title: ADJUVANT FORMULATION COMPRISING SUBMICRON OIL DROPLET EMULSION

DECLARATION OF GARY OTT, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

I, Gary Ott, hereby declare as follows:

1. I am currently employed by Chiron Corporation, 4560 Horton Street, Emeryville, California, where I have worked since 1986. I am currently a Senior Scientist in Vaccine Research. During my employment with Chiron Corporation, I have investigated the mechanism of action of emulsion adjuvants for vaccination, developed various adjuvant formulations, as well as synthesis and analytical assay techniques. I have worked extensively on the development of the MF59™ adjuvant, a commercial embodiment of a representative submicron oil-in-water emulsion as claimed in the above-identified application. This work included laboratory synthesis, assay development, production and analysis for clinical materials.

2. I received a B.A. in Chemistry, Magna cum Laude and a B.S. in Biological Sciences in 1969 from the University of California, Irvine. I received a Ph.D. in Biochemistry from the

University of Colorado in 1974. I have coauthored 33 papers relating to various topics including adjuvant technology. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

3. I am a coninventor of the above-identified patent application, U.S. Serial No. 08/418,870 ("the application"), and have read the Office Action dated January 31, 2000 ("Office Action"). I have also reviewed and am familiar with Woodard et al., *Vaccine* 3:137-145 (1985) ("Woodard"), and Silvestri et al., *International Journal of Pharmaceutics*, 50:141-146 (1989) ("Silvestri"), cited against the pending claims in the Office Action. In particular, the Office Action states that both of these references "deal with the desirability of making stable oil-in-water emulsions and teach how to vary the relevant parameters to achieve stability; one of the relevant parameters is droplet size." Office Action, page 3. However, I do not believe the invention is suggested by this combination of references. My opinion is based on the facts set forth below, as well as my familiarity with the subject matter.

4. In particular, the pending claims pertain to an adjuvant composition and methods of using the composition. The adjuvant composition consists essentially of a metabolizable oil, present in an amount of 0.5% to 20% of the total volume, and an emulsifying agent, present in an amount of 0.01% to 2.5% by weight (w/w). The oil and emulsifying agent are in the form of a submicron oil-in-water emulsion (i.e., an emulsion having oil droplets substantially all of which are about 100 nm to about 750 nm in diameter). The adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen.

5. As discussed with the Examiner in the interview of April 20, 2000, Woodard and Silvestri suggest fundamentally different emulsions than those emulsions claimed in the present application, both in physical constituents and in their mechanism of action. In particular, Woodard points out at page 139, Table 2, that stability is achieved with emulsifier concentrations of 4% or higher. The present composition, on the other hand, utilizes emulsifier concentrations of 0.01% to 2.5% by weight. Table 2 of Woodard suggests that when emulsifying agents are present at such low concentrations, heavy creaming (and hence lack of stability) occurs. Moreover, as explained in the interview and as illustrated in the attached Figures 1A and 1B, Woodard teaches that an antigen must be added to the internal phase (i.e., the oil phase in oil-in-water emulsions and the aqueous phase in water-in-oil emulsions), for optimal antibody

response; and that addition of the antigen to the external (continuous) phase reduces antibody production considerably (see Woodard, page 142, right column, 2nd paragraph). In order to "force" the antigen into the internal phase, the antigen is mixed with Woodard's oil and emulsifying agent prior to emulsification (mixing of the phases) which produces the submicron oil-in-water emulsion. See, e.g., page 139, right column, 3rd full paragraph. Thus, Woodard's submicron oil-in-water emulsion does not exist in the absence of antigen.

6. As discussed with the Examiner in the interview, Woodard formulates his adjuvant composition in this manner because the compositions are delivery systems designed to transport an antigen or another particle within the oil phase to antigen presenting cells (APCs). Thus, Woodard's compositions are used as vehicles for adjuvants. In contrast, the claimed adjuvant compositions, while capable of increasing the immune response to an antigen when administered with the antigen, does not contain an antigen. The claimed adjuvant compositions appear to work by direct stimulation or short term recruitment of APCs to the injection site.

7. Additionally, although Silvestri discloses that the stability of emulsions is improved by submicron size droplets, the reference does not pertain to adjuvants. Rather, the reference reiterates Woodard's teaching that the submicron emulsions are used as drug delivery systems to deliver drugs via the internal phase of the emulsion (see page 142, left column). As explained above, the emulsions in the claimed composition are not merely delivery systems, they act as adjuvants themselves.

8. Based on the foregoing, it is my opinion that the claimed compositions and methods of use are distinct from the emulsions disclosed in the cited references.

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 6/13/00

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Gary Ott, Ph.D.

EXHIBIT A

Curriculum Vitae

Name:	Gary Ott	
Date of Birth:	May 18,1947	
Place of Birth:	Long Beach, CA	
Education:	B.A. 1969 B.S. 1969	Chemistry Magna cum Laude Biological Sciences University of California, Irvine
	Ph.D. 1974	Biochemistry University of Colorado
Research and Professional Positions:	1969/1974	Research Associate Laboratory of Dr. William Bauer Dept. of Chemistry University of Colorado Boulder, CO
	1974/1978	Postdoctoral Fellow Laboratory of Dr. Walter Sauerbier Dept. of Genetics and Biophysics University of Colorado Health Sciences Center Denver, CO
	1978/1979	Automobile Mechanic Capitol Motors Denver, CO
	1979/1981	Postdoctoral Fellow Laboratory of Dr. Virgie Shore Biomedical Science Division Lawrence Livermore Laboratory Livermore, CA
	1981/1986	Scientist/Senior Scientist BioRad Laboratories Richmond, CA
	1986/present	Scientist/Senior Scientist Vaccine Research Chiron Corporation Emeryville, CA
Honors and Professional Societies:	Outstanding Undergraduate Chemist Award, UC Irvine – 1969 NDEA Predoctoral Fellow, University of Colorado – 1969-1972 PHI Lambda Upsilon Honor Society, University of Colorado – 1970-1974	
Professional interests:	1994/present	Research into the mechanism of action of emulsion adjuvants for vaccination. Development of biodegradable polymer adjuvant formulations (Synthesis and analytical assay development)

1990/1994	Development of the MF59 emulsion adjuvant for human vaccination (laboratory synthesis and assay development, scale-up and GMP production and analysis for clinical materials
1986/1990	Purification of viral glycoprotein antigens for human vaccination (laboratory purification and analysis, scale-up and GMP production and analysis of clinical materials.
1981/1986	Development of materials for separation of biological macromolecules (laboratory development and analysis, transfer to manufacturing, QC development)

Papers:

1. Ott, G., Ziegler, R., and Bauer, W.R. The DNA Melting Transition in Aqueous Magnesium Salt Solutions. *Biochemistry* **14**:3431, 1975.

2. Carlson, J., Ott, G., and Sauerbier, W. Transcriptional Organization of the Drosophila Melanogaster Ribosomal Genes. *J. Mol. Biol.* **112**:353, 1977.

3. Ott, G., Bastia, D., and Bauer, W.R. A Spectroscopic and Electron Microscopic Examination of the Highly Condensed DNA Structure Formed by Denaturation in $McC1O_4$. *Biochemica et Biophysica Acta.* **518**:216, 1978.

4. Giorno, R., Ott, G., and Sauerbier, W. Size Analysis of Heterogeneous Nuclear RNA in Aqueous Gel System. *Biochemica et Biophysica Acta.* **521**:235, 1978.

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21. O'Hagan, D.T., Ott, G.S., and Van Nest, G. Recent Advances in Vaccine Adjuvants: The Development of the MF59 Emulsion and Polymeric Microparticles. *Mol. Med. Today*, **3**:69, 1997.

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o/w emulsion

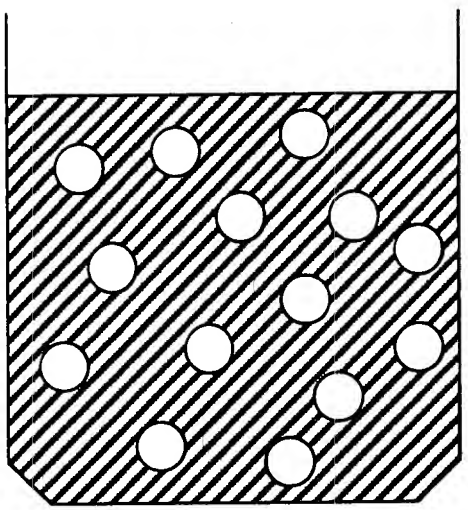

FIG. 1A

w/o emulsion

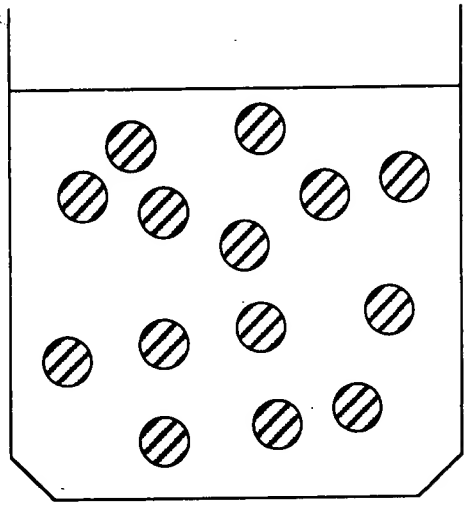

FIG. 1B